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Paper ~~98~~ 16

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

VENKATAKRISHNA SHYAMALA
(08/886,572),
Junior Party,

v.

JENNIFER L. HILLMAN
(5,756,332 and 09/007,306),
Senior Party.

Interference No. 104,436

Before SCHAFER, TORCZON, and LANE, Administrative Patent Judges.

TORCZON, Administrative Patent Judge.

JUDGMENT
(PURSUANT TO 37 CFR § 1.658)

INTRODUCTION

This interference relates to a protein in a cell signal transduction pathway. The pathway is implicated in cell response to environmental stress, including inflammation and apoptosis. Junior party Shyamala seeks to establish priority over senior party Hillman. Hillman rests on its accorded benefit date. We hold that Shyamala has not established priority over Hillman.

FINDINGS

[1] Shyamala identifies the protein that is the subject of this interference as MKK3-interacting protein (MIP) as shown in Shyamala's SEQ ID NO:1. MKK3 is a kinase in the p38 mitogen-activated protein kinase (MAPK) signal transduction pathway.

[2] Hillman identifies the protein as guanosine monophosphate reductase as shown in Hillman's SEQ ID NO:1.

[3] Count 2 is the sole count (Paper 72):

> A composition according to claim 1 of 5,756,332
>
> - OR -
>
> A composition according to claim 1 of 09/007,306.

[4] Claim 1 of Hillman's 332 patent is:

> An isolated and purified polynucleotide sequence encoding guanosine monophosphate reductase having the amino acid sequence of SEQ ID NO:1 or an amino acid sequence that is at least 95% homologous in sequence to the amino acid sequence of SEQ ID NO:1 and having guanosine monophosphate reductase activity.

[5] Claim 1 of Hillman's 306 application is:

> A substantially purified guanosine monophosphate reductase comprising the amino acid sequence of SEQ ID NO:1 or enzymatically active fragments thereof.

[6] Hillman's SEQ ID NO:1 is reproduced in the appendix to this decision.

[7] Shyamala's claims 1-3, 4, 5, 6, 9, and 10 of its 08/886,572 application correspond to Count 2.

[8] Hillman's claims 1, 2, and 4-9 of its 332 patent and claims 1 and 11 of its 306 application correspond to Count 2

[9] Hillman has been accorded a benefit date of 26 December 1996 for its constructive reduction to practice of an embodiment within the scope of Count 2.

[10] Shyamala has been accorded a benefit date of 1 July 1997 for its constructive reduction to practice of an embodiment within the scope of Count 2.

[11] When the interference was declared, Shyamala had also been accorded the benefit of two provisional applications:

- 60/021,641, filed 12 July 1996, and
- 60/021,224, filed 3 July 1996

[12] Hillman successfully attacked the benefit accorded to Shyamala for its provisional applications.

[13] If Shyamala were still entitled to that benefit, it would be senior party.

Shyamala's priority case

[14] Dr. Venkatakrishna Shyamala is the named inventor of the subject matter of the Shyamala claims.

[15] According to Dr. Shyamala, she began working on proteins that interact with MKK3 in 1994 [1025[1] at 3].

[16] According to Dr. Shyamala, she was interested in MKK3 because it was known to regulate the activity of p38 kinase, which itself was implicated in biological pathways of clinical interest [1025 at 3].

[17] According to Dr. Shyamala, little was known about proteins interacting with MKK3 other than p38 kinase [1025 at 3].

[18] Hamiduddin "Hamid" Khoja was Dr. Shyamala's assistant at the relevant time [1025 at 4-5].

[19] Mr. Khoja declared that he no longer works for Chiron and has no interest in the outcome of the interference [1010 at 2].

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[1] Declaration of Venkatakrishna Shyamala, Ph.D.

[20] Dr. Shyamala directed Mr. Khoja to screen thousands of proteins randomly selected from a protein library to identify proteins interacting with MKK3 [1025 at 4-5; 1010[2] at 3].

[21] The screening involved inserting test sequences of complementary deoxyribonucleic acid (cDNA) into yeast to produce test proteins and identifying successful interactions of test proteins with MKK3 by a change in color [1025 at 4].

[22] According to Mr. Khoja, he analyzed the DNA of clones that demonstrated successful interactions [1010 at 3].

[23] A 20 February 1996 entry in Mr. Khoja's Notebook No. 7613 shows photographs of two gels sorting insert cDNAs by size [1010 at 4; 1012 at 137].

[24] According to Shyamala and Khoja, he identified several clones with 1.4 kilobase (kb) inserts of cDNA as being of interest [1010 at 4; 1025 at 6].

[25] According to Mr. Khoja, the run in the lower photograph labeled B73 proved to code for what was later identified as MIP [1010 at 4].

[26] Shyamala does not explain why, on 20 February 1996, 1.4 kb proteins were of particular interest or what significance Shyamala or Khoja ascribed to B73 on that date.

[27] Mr. Khoja requested sequencing of clone 14b, which he states was B73 [1010 at 4].

[28] The notebook of Chun Ting Lee-Ng shows five forms labeled "Request for DNA Sequence" from Hamid Khoja, one of which (top right) lists "14B". The requests are initialed as received 26 February 1996 [1014[3] at 163].

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[2] Declaration of Hamiduddin Khoja.

[3] Lee-Ng Notebook No. 7468.

[29] Mr. Khoja declared [1010 at 5] that he believes the computer-generated sequence [1015] titled "Translation of DNA 14b_comp.seq" and dated "Thu Mar 21 14:39:36 1996" is a print out of the tested DNA for clone 14b with undated annotations in his handwriting and Dr. Shyamala's handwriting.

[30] Mr. Khoja states that "Dr. Shyamala and I determined that the insert in clone 14b encoded only part of a protein, because the 14b insert did not contain sequences encoding the amino acid methionine, which initiates all protein sequences" [1010 at 5].

[31] In the computer translation [1015], all three of the computer-generated polypeptide sequences have at least one methionine before a stop codon.

[32] According to Mr. Khoja, he isolated the remaining 5' cDNA sequence associated with the 14b DNA sequence and submitted it to Ms. Lee-Ng for sequencing on 16 May 1996 [1010 at 5-6; 1016[4] at 49].

[33] Mr. Khoja states [1010 at 6] that the sequence listing titled "14bcom ed Translated Sequence" and dated 23 May 1996 [1017] is the sequence for one of the clones he submitted because it is dated one week after he submitted the clones for sequencing, because it contains the 11 missing amino acids, and because it has a 38 nucleotide overlap with the earlier partial sequence [1015].

[34] Mr. Khoja does not explain how he knows there were 11 missing amino acids or why he believed Exhibit 1017 shows the missing amino acids.

[35] Nucleotides 16-77 of the March sequence [1015] overlap with nucleotides 200-261 of the May sequence [1017].

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[4] Lee-Ng Notebook No. 8093.

[36] According to Dr. Shyamala, the "com" notation in the title of the sequence indicates that it is complete and the "ed" notation means that the sequence was edited [1025 at 7].

[37] According to Mr. Khoja, the printout entitled "MIK nt Translated Sequence" dated 14 June 1996 [1018] was generated by aligning and then combining of the two earlier sequences.

[38] According to Mr. Khoja he prepared a full-length DNA clone at Dr. Shyamala's request, which was then submitted for sequencing [1010 at 7; 1016 at 103].

[39] Mr. Khoja had also experimentally verified that the 14b clone interacted with MKK3 [1010 at 7-8; 1012 at 179].

[40] Mr. Khoja had also localized the DNA in question to human chromosome 14 [1010 at 8; 1012 at 175].

[41] Mr. Khoja determined, using western blot analysis, that the 14b protein had a molecular weight of about 40 kilodaltons (kD) and noted a high level of expression for the protein. According to Mr. Khoja, in this instance he was referring to the full-length 14b clone [1010 at 8; 1013 at 5].

[42] Mr. Khoja noted two undated BLAST alignments showing 76.7% and 79.2% homology between the putative MIP sequence and two other known proteins: guanosine monophosphate reductase (gmg) and glucose-6-phosphate dehydrogenase (hg6pd1), respectively [1010 at 9; 1020; 1019].

[43] According to Dr. Shyamala, in May 1996 she further characterized the expression pattern for the partial 14b clone by using 14b cDNA hybridization with messenger ribonucleic acid (mRNA) to identify MIP expression in various tissues [1025 at 10-11; 1024 at 43].

[44] Page 42 of Dr. Shyamala's notebook indicates that both 14b and "G3PDH" were to be analyzed [1024 at 42].

[45] Page 43 of Dr. Shyamala's notebook shows two northern blots showing the results of the tissue expression analysis [1024 at 43]. The one on the left is labeled "G3PDH". The one on the right is unlabeled, but appears above a printout labeled "G3PDH".

[46] "G3PDH" is not defined. Note that glucose-6-phosphate dehydrogenase (hg6pd1) was identified as a protein with about 80% homology to MIP.

[47] The right northern blot shows strong expression for B, K, Li, P, and Sp; some expression for Lu; little expression for M; and no expression for H at between 1.4 kb and 2.4 kb [1024 at 43].

[48] The left northern blot shows strong expression for B, K, Li, Sp, and M; but little or no expression for H, Lu, or P at between 1.4 kb and 2.4 kb [1024 at 43].

[49] According to Dr. Shyamala, the abbreviations mean heart (H), brain (B), kidney (K), liver (Li), lung (Lu), pancreas (P), spleen (S) [sic, Sp?], and striated muscle (M) [1025 at 10-11].

[50] Based on this data, Dr. Shyamala concluded that MIP expression shows tissue specificity [1025 at 11].

[51] Hillman did not cross examine any of Shyamala's priority witnesses.

[52] Despite some inconsistencies and gaps in the narrative, we deem the testimony of Dr. Shyamala and Mr. Khoja to be essentially credible for the purposes of this decision.

[53] In deciding Hillman Preliminary Motion 1, the Board determined that claims 1, 4, 6, and 10 did not lack utility under 35 U.S.C. 101, based on Example 5, which corresponds to Shyamala's method-of-use claim 6.

[54] In deciding Hillman Preliminary Motion 2, the Board determined that Shyamala had not identified a utility for MIP, other than its interaction with MKK3, in its two provisional applications.

[55] The filing for Shyamala's involved 572 application and the accorded benefit date for Shyamala is 1 July 1997.

[56] Its provisional applications were filed in 1996.

The state of the art at and after Shyamala's filing date

[57] The Herlaar review article[5] [1004] was published October 1999.

[58] Herlaar confirms that, at least in 1999, that the p38 MAPK signaling pathway is one of many pathways of clinical interest because of their relation to inflammatory diseases [1004 at 439:L[6]].

[59] Herlaar identifies MKK3 to be one of four kinases that activate p38 MAPK [1004 at 440:Fig. 1].

[60] Herlaar confirms that "protein kinases have become important targets for drug therapy" [1004 at 445:L], but focuses on synthetic inhibitors of p38 MAPK itself rather than a protein targeting an intermediate kinase [1004 at 445:L-446:L].

[61] In the concluding remarks, Herlaar focuses on the continuing uncertainty in understanding inflammatory pathways generally, and p38 MAPK[7] pathways in human cell lines in particular [1004 at 446:L].

[62] Herlaar offers five "outstanding questions" [1004 at 446:L]:

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[5] E. Herlaar & Z. Brown, "p38 MAPK signalling cascades in inflammatory disease", 5 Mol. Med. Today 439 (Oct. 1999) (Herlaar). The authors are affiliated with Novartis Horsham Research Centre.

[6] Page:column, in this case left column.

[7] Among other complications, the paper discusses five separate isoforms for "p38 MAPK". The p38α isoform is one of three isoforms activated by MKK3.

- Are kinases in general a good target for drug discovery?
- Which p38 MAPK isoform(s) play(s) a crucial role in immune and inflammatory cells?
- What role does p38 MAPK play in NF-κB-dependent transcription?
- What role does JNK play during inflammation?
- Can specific inhibitors be developed to target the p38α isoform without toxicity?

[63] In view of Herlaar, we find that as late as 1999 researchers were still trying to elucidate MAPK pathways, identify relationships between kinases in the pathway, and identify inhibitors for those kinases, but that the research was still marked by considerable uncertainty.

[64] The Lee article[8] [1005] was published in 1999.

[65] Lee confirms that, at least in 1999, p38 MAPK inhibitors were believed to be "efficacious in several disease models, including inflammation, arthritis and other joint diseases, septic shock, and myocardial injury" [1005, abstract].

[66] Lee notes the identification of four p38 homologs (α, β, γ, and δ) in 1996-97 [1005 at 390:R].

[67] Lee further notes that in 1997-1998, the art found that MKK3 selectively activates p38α and p38γ, while MKK6 activates all four p38 isoforms. MKK4 activates p38 and another kinase [1005 at 390:R].

[68] According to Lee, several substrates had been identified for p38 *in vitro*, only a few substrates (and only for p38α) had been identified *in vivo* [1005 at 390:R].

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[8] J.C. Lee et al., "p38 Mitogen-Activated Protein Kinase Inhibitors—Mechanisms and Therapeutic Potentials", 82 Pharmacol. Ther. 389 (1999) (Lee). The authors are with SmithKline Beecham Pharmaceuticals.

[69] Substrate means a molecule on which an enzyme acts.[9]

[70] Lee notes that "a number of [gene] transcription factors are phosphorylated *in vitro* by p38, [but] the physiological relevance of this phosphorylation is unknown [1005 at 391:R].

[71] Lee reports regarding a protein called ATF2 that [1005 at 391:R]:

> [w]hile it is an excellent *in vitro* substrate for p38 and other isoforms, it is not clear if ATF2 is a physiological substrate of p38α since the transcriptional activation or phosphorylation-mediated mobility shift in ATF2 has not been correlated yet with pharmacological inhibition of p38 MAPK.

[72] A synthetic p38 MAPK inhibitor is reported to have been used in 1998 in an *in vivo* model of angiogenesis [1005 at 392:L] and in 1996 in an *in vivo* model of TNF-α-mediated inflamation, endotoxin-induced shock, arthritis, and parathyroid hormone-induced bone resorption [1005 at 394:L-395:R].

[73] Lee indicates that in 1999, the p38 MAPK-inhibition art was still marked by considerable uncertainty, particularly in translating *in vitro* suggestions into *in vivo* results, and was only just beginning to bear therapeutic fruit for one of a class of synthetic p38 kinase inhibitors.

[74] The McLaughlin article[10] [1006] was published on 5 April 1996.

[75] According to McLaughlin, CSBP is a synonym for p38 [1006 at 8488:R].

[76] According to Herlaar, by 1999 CSBP was associated with one isoform of p38 [1004, Table 1].

[77] McLaughlin reports that p38 is activated by MKK3 and MKK4 in response to stress and activated by a number of other environmental factors, including TNF [1006 at 8488:R].

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[9] B. Alberts et al., Molecular Biology of the Cell at G-22 (3d ed. 1994).

[10] M.M. McLaughlin et al., "Identification of Mitogen-activated Protein (MAP) Kinase-activated Protein Kinase-3, a Novel Substrate of CSBP p38 MAP Kinase", 271 J. Biol. Chem. 8488 (1996) (McLaughlin). The authors are with SmithKline Beecham Pharmaceuticals. Two of the authors are also listed as authors on the Lee article.

[78] According to McLaughlin, inhibition of p38 could block certain inflammatory processes and "has been implicated in the apoptosis of neurons upon growth factor removal" [1006 at 8488:R].

[79] Apoptosis means programmed cell death:[11] a cell's inherent, inducible self-destruction mechanism.

[80] McLaughlin reports using a yeast two-hybrid screen, like Shyamala's, to identify other proteins that interact with p38 [1006 at 8488:R].

[81] McLaughlin isolated a protein that interacted with, and appeared to be a substrate of, p38 [1006 at 8488:L].

[82] McLaughlin did not suggest a use for its protein.

[83] McLaughlin suggests that in April 1996, the search for proteins interacting with p38 was a hot research area and that the use of yeast two-hybrid systems to conduct the search was a standard approach to the problem.

[84] The Han article[12] [1007] was published in 1994.

[85] Han reports that mammalian cells phosphorylate p38 in response to lipopolysaccharide endotoxins from Gram-negative bacteria [1007 at 808].

[86] Han also reports that p38 is also phosphorylated in response to increases in extracellular osmolarity [1007 at 809], a type of cellular stress.

[87] Han does not indicate a practical use for p38.

[88] Han confirms that p38 was a subject of research interest.

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[11] B. Alberts et al., Molecular Biology of the Cell at G-3 (3d ed. 1994).

[12] J. Han, L.-D. Lee, L. Bibbs & R.J. Ulevitch, "A MAP Kinase Targeted by Endotoxin and Hyperosmolarity in Mammalian Cells", 265 Science 808 (5 Aug. 1994) (Han). The Han authors are with the Scripps Research Institute.

[89] The Xia article[13] [1008] was published in 1995.

[90] Xia is the paper McLaughlin cites for the proposition that p38 is "implicated in the apoptosis of neurons upon growth factor removal".

[91] Xia confirms that the "processes of both cell survival and cell death involve highly regulated signaling pathways that are currently the subject of intense investigation" [1008 at 1326].

[92] Xia reports that as of 1995 many proteins had been identified that prevent or induce apoptosis [1008 at 1326].

[93] Xia confirms that p38 was known to have a role in apoptosis in response to environmental stresses, but that its precise function was unknown [1008 at 1326].

[94] Xia tested the effect of p38 activation apart from the activation of a different kinase by modulating the expression of variant MKK3 enzymes, which specifically activate p38 and concluded that MKK3 activation of p38 is sufficient to induce apoptosis [1008 at 1328-30].

[95] Xia concluded, however, that the field was still wide open to further study [1008 at 1330]:

> Because there are many mechanisms for the regulation of the relevant MAP kinase pathways and various forms of cross talk between these signal transduction pathways probably exist, the decision for cellular life or death may depend on the integration of multiple signals. It is possible that the mechanisms proposed here function generally in the control of apoptosis in both neuronal and non-neuronal cells.

[96] The Raingeaud article[14] [1009] was published in March 1996.

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[13] Z. Xia, M. Dickens, J. Raingeaud, R.J. Davis & M.E. Greenberg, "Opposing Effects of ERK and JNK-p38 MAP Kinases on Apoptosis", 270 Science 1326 (24 Nov. 1995) (Xia). The authors are with Harvard Medical School or the Howard Hughes Medical Institute and the University of Massachusetts Medical School.

[14] J. Raingeaud, A.J. Whitmarsh, T. Barrett, B. Dérijard & R.J. Davis, "MKK3- and MKK6-Regulated Gene Expression Is Mediated by the p38 Mitogen-Activated Protein Kinase Signal Transduction Pathway", 16 Mol. & Cellular Biol. 1247 (Mar. 1996) (Raingeaud). The authors are with the Howard Hughes Institute and the University of Massachusetts Medical School. Two also appear on the Xia paper.

[97] Raingeaud notes that p38 is part of one of several signaling pathways that are activated in response to cytokines and environmental stress, which makes isolating the function of p38 difficult [1009 at 1247:R].

[98] Raingeaud confirmed that MKK3 appears to activate p38 selectively, but could not rule out the possibility that other kinases are also involved [1009 at 1249:R-1250:L].

[99] Raingeaud cautioned that experimental overexpression of p38 could result in p38 MAP kinase phosphorylation of proteins that are not ordinarily substrates for p38 [1009 at 1250:L].

[100] Raingeaud also confirmed that MKK6 appears to activate p38 selectively [1009 at 1252].

Diagnostic and therapeutic utilities

[101] Shyamala points to the following disclosure of diagnostic and therapeutic utilities in its provisional applications to establish utility [1029 at 4:1-10]:

> Still another embodiment is a method of diagnosis of a disease in a patient characterizable by aberrant MIP polypeptide mediated activity including one selected from the group consisting of MKK3 associated activity and GTP mediated cellular response by providing a MIP antibody, contacting a patient tissue sample with the antibody, and detecting the amount of the MIP polypeptide present.
>
> Another embodiment of the invention is a method of treating a disease in a patient characterizable by aberrant MIP polypeptide mediated activity including one selected from the group consisting of MKK3 associated activity and GTP mediated cellular response by providing inhibitor MIP, and administering to the patient a sufficient amount of the inhibitor to effect a reduction in MIP polypeptide mediated signaling within a population of cells.

[102] Shyamala elaborated on these methods later in the provisional applications [1029 at 33:9-26]:

> MIP may be useful in a diagnostic context for identifying overexpression of MIP by identifying MIP transcript in brain or spleen tissues, in the presence of a condition characterized by abnormal activation of the p38 MAPK stress signal transduction pathway. Additionally, genetic information of MIP may be useful for

> design of a therapeutic based on modulating MIP polypeptide activity, affecting MIP gene expression, expressing genetic variants of MIP for therapeutic effect such as mimicry of MIP activity or modulation of MIP activity, for example inhibition of MIP activity, for the purpose of affecting a MIP mediated pathway, for example an MKK3 activation pathway, or a p38 MAPK signal transduction activation pathway.
>
> Gene therapy techniques can be applied in the invention for treatment of a disease characterizable by excessive MIP polypeptide mediated MKK3 activation, or MIP polypeptide mediated p38 MAPK signal transduction pathway activation using a genetic variant of MIP, for example a dominant negative MIP polypeptide or by using a peptide inhibitor of MIP activity, for example inhibitors of MIP binding to MKK3. The polynucleotide encoding the MIP polypeptide, the MIP polypeptide variant, or an inhibitor of MIP activity may be engineered for administration by a gene therapy protocol, provided the polynucleotide encoding for example, the dominant negative or the modulator or inhibitor is capable of expression in a patient.

[103] Shyamala did not, at the time of filing the provisional applications, identify any

- disease in a patient characterizable by aberrant MIP polypeptide mediated activity;
- condition diagnostically associated with overexpression of MIP by identifying MIP transcript in brain or spleen tissues; or
- condition treatable by modulating MIP polypeptide activity, affecting MIP gene expression, or expressing genetic variants of MIP for therapeutic effect.

[104] Rather than simply lacking knowledge of the mechanism by which MIP works in disease or other medical conditions, Shyamala failed to identify a disease or medical condition for which MIP is known to have a role.

[105] We find no connection between these disclosures and a known real-world utility at the time of filing. Shyamala's repeated use of "may" to describe these utilities is telling because it shows that they are not grounded on actual knowledge.

Reconsideration of the Board's decision on Shyamala's benefit

[106] Shyamala was ordered to file "any request for reconsideration...within twenty-one (21) days of the date of" the decision on motions.

[107] No request for reconsideration was filed within that time period.

[108] Shyamala points (Paper 89 at 26-27) to its exhibits 1004-1009 and its disclosures as establishing error in the decision motions, but does not point to a specific finding or conclusion deemed to be in error or to a specific part of the record that shows why the finding or conclusion is in error.

[109] Shyamala contends that the Board recognized a utility, as a tissue assay, for at least some of Shyamala's claims (Paper 89 at 28).

[110] The Board held that Hillman had not established a lack of utility for the invention of Shyamala claim 6 (Paper 71, F44-F50) and, by extension, for Shyamala claims 1 and 10.

[111] The Board specifically rejected as unsupported Shyamala's contention that it had a utility linked to the interaction of MIP and MKK3 (Paper 71, F51-F53).

[112] Dr. Shyamala's declaration recounts the use of a northern blot assay to determine tissues in which MIP is expressed [1025 at 10-11].

[113] Dr. Shyamala's declaration [1025 at 10-11] does not disclose a method of identifying tissue based on differential MIP expression. It shows the opposite: that starting with a small sample of known tissues, Shyamala could determine whether those tissues express MIP under a specific set of conditions.

[114] Dr. Shyamala does not go so far as to declare that the northern blot experiment was the basis for a useful tissue-identification assay.

[115] Assuming that Dr. Shyamala believed she was inventing a tissue assay, it is not clear given the very small sample of possible tissues and the limited information produced (relative MIP expression level) that anyone of ordinary skill in the art would have considered such an assay to have a credible utility.

[116] Shyamala did not disclose a method for determining tissue type until filing the involved application; that is, Shyamala did not disclose the method in the provisional applications.

[117] Instead, as previously noted, Shyamala's provisional applications speculated that MIP overexpression could be used to diagnose a disease [1029 at 33:9-26].

[118] Shyamala does not offer an explanation for the gap between the putative invention of the tissue assay and its eventual first disclosure in Shyamala's involved application.

[119] According to Shyamala (Paper 89 at 29), assays including the tissue expression assay were disclosed in the provisional applications.

[120] Shyamala provisionally disclosed [1029 at 4:1-5]:

> Still another embodiment is a method of diagnosis of a disease in a patient characterizable by aberrant MIP polypeptide mediated activity including one selected from the group consisting of MKK3 associated activity and GTP mediated cellular response by providing a MIP antibody, contacting a patient tissue sample with the antibody, and detecting the amount of the MIP polypeptide present.

[121] This disclosure does not teach a tissue assay. Instead, it speculates that one could assay for an unidentified disease characterized by aberrant MIP activity.

[122] Shyamala provisionally disclosed [1029 at 5:8-12]:

> Any portion of the MIP gene is useful as a probe for MIP transcription activation in a tissue blot or for analysis of cells expressing MIP under, for example, regulatable conditions, or as a diagnostic probe for a MIP-associated

> condition, for example a condition associated with p38 MAPK activation or a condition associated with NADPH oxidase activation or inactivation.

[123] This disclosure does not teach a tissue assay. Instead, it speculates that one could probe for an unidentified disease associated with MIP.

[124] Shyamala provisionally disclosed [1029 at 5:25-26]:

> Northern blot analysis of the tissue specific expression of MIP indicates a 2,000 nucleotide transcript in spleen and brain tissues.

[125] This disclosure does not teach a tissue assay. Instead, it reports the presence of MIP in brain and spleen tissues. The presence of MIP in these tissues is not cited as the basis for a tissue-typing assay, nor is the presence of MIP in these tissues associated with a disease.

[126] Shyamala provisionally disclosed [1029 at 27:8-15]:

> The antibodies generated in this manner can be used in any conventional applications, including for diagnostic and therapeutic purposes. For example, as a diagnostic, it can be used in an immunoassay for identification or detection of an MIP polypeptide or a homolog thereof in a sample suspected of containing such. For this purpose, the antibodies can be labeled with a suitable marker, such as a radioactive label, and allowed to react with the sample. After an appropriate length of time, the sample can be examined for the presence of specific binding pairs. Presence of specific binding suggests that an MIP polypeptide or a homolog thereof is present in the sample.

[127] This disclosure does not teach a tissue assay. Instead, it reports that antibodies can be raised against MIP and used for the conventional uses of such antibodies. No diagnostic, therapeutic, or labeling utility is actually identified.

[128] None of the uses Shyamala identified in the provisional applications appear to rise above generalized speculation about what uses MIP might eventually be shown to have.

Hillman's priority case

[129] Hillman rests on its accorded constructive reduction to practice, 26 December 1996, which is the filing date of its involved patent (Paper 79).

[130] The notice (Paper 79) announcing Hillman's intent to rest on its accorded constructive reduction to practice was filed during the priority phase of the interference.

[131] Hillman's benefit date is the filing date of Hillman's 08/774,169 application, which issued as Hillman's 332 patent.

[132] Hillman's involved 306 application is a divisional application of Hillman's 169 application.

[133] The administrative patent judge administering the interference set times for filing preliminary motions (Paper 19).

[134] A preliminary motion may be filed to attack accorded benefit. 37 C.F.R. § 1.633(g).

[135] Shyamala did not file a motion attacking Hillman's entitlement to its accorded benefit.

[136] Shyamala did not file a motion for judgment that Hillman's involved claims are unpatentable for lack of support under 35 U.S.C. 112[1].

[137] Shyamala would now like to attack Hillman's accorded benefit [Paper 89 at 30].

[138] Shyamala already had its opportunity to attack Hillman's accorded benefit.

[139] Shyamala correctly notes that the specifications of Hillman's involved application and patent are identical [Paper 89 at 30].

[140] The involved Hillman application has the benefit of the Hillman patent, which issued from the involved application's parent. In short, Hillman's accorded benefit date is the filing date of the involved Hillman patent.

DISCUSSION

The senior party benefits from a rebuttable presumption that it was the first to invent. At the final hearing, the junior party bears the ultimate burden of persuasion in overcoming that presumption. 37 C.F.R. § 1.657(a). The ultimate burden remains with the junior party and does not shift with the burden of production. Brown v. Barbacid, 276 F.3d 1327, 1332, 61 USPQ2d 1236, 1239 (Fed. Cir. 2002).

Shyamala's conception of the subject matter of the count

Conception is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is later applied in practice. Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). If, as here, the count does not recite a specific utility, evidence of any utility is sufficient. Cross v. Iizuka, 753 F.2d 1040, 1045, 224 USPQ 739, 744 (Fed. Cir. 1985).

For the purposes of this decision, we can assume that all of Shyamala's facts regarding its conception of the invention through 14 June 1996 are true. Shyamala has not, however, pointed us to evidence showing that even as of the putative date of Shyamala's actual reduction to practice, the inventor had a specific, concrete application for the MIP protein in mind, much less a definite and permanent idea of how it would be used in practice. Rather, the evidence is consistent with a research program to elucidate the function of a protein associated with a cellular signaling pathway of great interest. We see no evidence that Shyamala had any application in mind as of the putative date of conception.

As the Supreme Court observed with regard to utility: "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Brenner v. Manson, 383 U.S. 519, 536 (1966). In Manson, the inventor claimed a process for making a steroid. The steroid so produced had no known use, but was homologous to a known useful steroid. The inventor contended that, in addition to this homology, the process was useful "if it produces a compound whose potential usefulness is under investigation by serious scientific researchers". Id. at 531. The Court recognized these contentions as presenting "the basic problem" for it to adjudicate. Id. at 532. The Court rejected the homology argument based on the conceded unpredictability of the steroid art. Id. After much consideration, the Court rejected the "potential usefulness" standard as contrary to public policy "[u]nless and until [the invention] is refined and developed to this point--where specific benefit exists in currently available form". Id. at 534-35.

Shyamala's invention is distinguishable from Manson's in that Shyamala claims 1, 4, and 10 are directed to compositions and Shyamala claim 6 is directed to a method of use, while Manson was claiming a method of making. If anything, however, Shyamala is in an even weaker position than Manson. Manson could point to a pre-filing journal article to show that a close homolog was known to have a utility. Id. at 522. Shyamala's evidence, by contrast, suggests that the p38 MAPK pathway is still the subject of intense research with few concrete results—and those results come from synthetic inhibitors completely different from Shyamala's MIP.

Shyamala correctly notes that an inventor need not know the mechanism underlying its invention (Paper 89 at 26[15]). The problem here, however, is more fundamental than simply not knowing the mechanism underlying the diagnosis or treatment of a disease. No specific disease was linked to MIP expression in the disclosure. A utility for MIP cannot piggyback on known roles for p38 without, at a minimum, a correlation between MIP and some p38 MAPK pathway disease or condition. Shyamala's disclosures and briefing speculated that such a correlation may exist, but Shyamala has yet to disclose any such correlation. Consequently, we cannot find that Shyamala conceived of a use for MIP.

Shyamala is mistaken in its belief that the Board had previously found that some Shyamala claims had utility. Instead, the Board held that neither side had carried its burden of proof on the utility of Shyamala's claims. The ultimate burden was on Hillman as the movant to establish that Shyamala lacked utility, so in the absence of any showing on the merits with regard to Shyamala's claim 6, the motion was denied with respect to claim 6 and claims that could benefit from the purported utility of claim 6. Shyamala cannot transform a failure of proof by Hillman into a proof of utility for Shyamala.[16]

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[15] Citing Newman v. Quigg, 877 F.2d 1575, 11 USPQ2d 1340 (Fed. Cir. 1989); Fromson v. Adv. Offset Plate, Inc., 720 F.2d 1565, 219 USPQ 1137 (Fed. Cir. 1983); Cross, 753 F.2d 1040, 224 USPQ 739.

[16] The concurrence would have us find Shyamala's claims unpatentable for lack of utility. The time to decide that motion was during the preliminary motions period. Hillman did not carry its burden. Given the decision on priority, it is unnecessary, as well as inappropriate, to reach this issue now.

Shyamala's provisional applications

In seeking reconsideration[17] of the original Board decision stripping Shyamala of the benefit of its provisional applications, Shyamala must show how the Board erred in its decision. Shyamala relies on its exhibits 1004-1009 to support the speculative attributes of Shyamala's invention. The problems with this approach are twofold. First, the articles dated after the filing dates of the provisional applications are not probative of what one skilled in the art would have understood from them at the time the applications were filed. If anything, the articles suggest that the field is still very much in an early exploratory phase, in which the few successful leads are very different from Shyamala's MIP. Second, the articles do not discuss the significance of Shyamala's MIP. While it is quite apparent that the p38 MAPK pathway is of intense interest because of its role in many medical conditions, neither the articles nor Shyamala elucidate any significant role for MIP in that pathway or correlate MIP to any disease condition.

Shyamala's argument that the provisional applications disclose the tissue-typing invention of claim 6 are also unpersuasive. While the provisional applications mention the northern blot experiment that appears to be the ultimate inspiration of the tissue-typing claim, they do not provide a credible basis for the claim. The northern blot experiment, if anything, establishes the reverse: given known tissue samples (not said to suffer from any disease), it is possible to determine a relative level of MIP mRNA expression (including no expression). This showing is a far cry from a claim that relative levels of MIP mRNA expression would provide a useful way

[17] Shyamala should have sought reconsideration sooner (Paper 71 at 29). Ordinarily, the decision on preliminary motions should decide all questions about the scope of the count and the benefit accorded to the parties to avoid the expense to the parties of having to prove multiple contingencies during the priority phase of the proceeding.

of identifying unknown tissues. Among other problems, the record does not disclose more than one instance of the experiment having been run. Thus, the utility of the claim rests on a single data point at a single time for each tissue. Shyamala contends that MIP is part of a signaling pathway, which strongly suggests that MIP expression will depend on factors other than simply the tissue type, such as whether the tissue is in a state or environment that induces the signaling pathway. Given the large number of variables and the unpredictability of the art, too little data existed to extrapolate a tissue-typing assay from a single northern blot experiment. The fact that Shyamala did not even describe the assay until its third filing confirms our finding that Shyamala did not possess the tissue-typing assay when the two provisional applications were filed.

Hillman's priority case

Since the junior party has the ultimate burden of establishing priority, a senior party may rest its priority case on its accorded benefit for constructive reduction to practice. E.g., Griffin v. Bertina, 285 F.3d 1029, 1031, 62 USPQ2d 1431, 1432 (Fed. Cir. 2002) (noting that the senior party "elected to rely on his accorded benefit date...rather than attempt to establish an earlier priority date"). This is consistent with the practice that the junior party always bears the ultimate burden of proof on priority.

During the preliminary motion phase, a party may file a motion to attack the benefit of a constructive reduction to practice accorded to an opponent. 37 C.F.R. § 1.633(g). Hillman successfully attacked Shyamala's accorded benefit to its provisional applications. Shyamala did not attack the benefit accorded to Hillman.

Hillman's earliest constructive reduction to practice is the filing of the application that issued as Hillman's involved patent. The disclosures of both Hillman's involved application and patent are substantially the same. The count includes two of Hillman's claims. Consequently, if Hillman had support for the Hillman claims comprising the count, it is unlikely that Shyamala could have successfully attacked Hillman's accorded benefit.[18] Note that Hillman did not file a preliminary motion attacking Hillman's support for the claims comprising the count.

Shyamala now contends that it has not had an opportunity to attack Hillman's accorded benefit. That contention is simply untrue. Shyamala contends that it is unprecedented for Shyamala to be deprived of a chance to "reply" to Hillman's priority case. The converse is true. It would be unprecedented for Shyamala to reply to a notice from Hillman stating that it is not putting on a priority case. Hillman has alleged nothing to which Shyamala could reasonably expect to reply.

Shyamala alleges a procedural irregularity and points to 37 C.F.R. § 1.633(a), which forbids an attack on priority in the form of a preliminary motion. This argument overlooks the express authorization to attack accorded benefit in 37 C.F.R. § 1.633(g). The point of the preliminary motions period is to establish the count and the accorded benefit to simplify the proofs of priority required in the priority phase of the interference. If a party could put on a full priority case in the preliminary motions, it would frustrate the purpose of preliminary motions in most cases. The exception, however, is accorded benefit, which is simply another name for the earliest constructive reduction to practice in the form of a patent filing with a chain of continuity

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[18] Hillman only needs a single described and enabled embodiment within the scope of the count. Weil v. Fritz, 572 F.2d 856, 866 n.17, 196 USPQ 600, 608 n.17 (CCPA 1978).

leading to an involved application or patent. An attack on accorded benefit proceeds from the benefit document itself (in a manner analogous to, but not identical with, attacking benefit under 35 U.S.C. 120). It does not require the sort of elaborate proofs customary in establishing an actual reduction to practice (or conception, or diligence, or abandonment, suppression, and concealment). Moreover, the constructive reduction to practice date is often a necessary element in establishing diligence or abandonment, suppression, and concealment. Consequently, it is precisely the sort of issue that is best pinned down during the preliminary motions phase. In any case, that is where the interference rules have placed such attacks. It can hardly have been irregular for the Board to follow its rules and regular procedure.

ORDER

Upon consideration of the briefs of the parties, it is:

ORDERED that judgment on priority as to Count 2 is awarded against junior party Shyamala;

FURTHER ORDERED that Shyamala is not entitled to a patent containing claims 1-3, 4, 5, 6, 9, and 10 of its 08/886,572 application, which correspond to Count 2;

FURTHER ORDERED that a copy of this decision be given a paper number and be entered in the administrative record of Shyamala's 08/886,572 application, Hillman's 09/007,306 application, and Hillman's 5,756,332 patent; and

FURTHER ORDERED that any further mail to the Board in this proceeding be sent to the post office box indicated on the first page of this decision.

RICHARD TORCZON
Administrative Patent Judge

SALLY GARDNER LANE
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

INTERFERENCE TRIAL SECTION

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Notice: Any agreement or understanding between parties to this interference, including any collateral agreements referred to therein, made in connection with or in contemplation of the termination of the interference, shall be in writing and a true copy thereof filed in the United States Patent and Trademark Office before termination of the interference as between said parties to the agreement or understanding. 35 U.S.C. 135(c); 37 C.F.R. § 1.661.

APPENDIX

Hillman SEQ ID NO:1:

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Met Thr Cys Cys Leu Pro Ala Leu Arg Phe Ile Ala Thr Pro Arg Leu
1               5                  10                  15
Ser Ala Met Pro His Ile Asp Asn Asp Val Lys Leu Asp Phe Lys Asp
            20                  25                  30
Val Leu Leu Arg Pro Lys Arg Ser Thr Leu Lys Ser Arg Ser Glu Val
        35                  40                  45
Asp Leu Thr Arg Ser Phe Ser Phe Arg Asn Ser Lys Gln Thr Tyr Ser
    50                  55                  60
Gly Val Pro Ile Ile Ala Ala Asn Met Asp Thr Val Gly Thr Phe Glu
65                  70                  75                  80
Met Ala Lys Val Leu Cys Lys Phe Ser Leu Phe Thr Ala Val His Lys
                85                  90                  95
His Tyr Ser Leu Val Gln Trp Gln Glu Phe Ala Gly Gln Asn Pro Asp
            100                 105                 110
Cys Leu Glu His Leu Ala Ala Ser Ser Gly Thr Gly Ser Ser Asp Phe
        115                 120                 125
Glu Gln Leu Glu Gln Ile Leu Glu Ala Ile Pro Gln Val Lys Tyr Ile
    130                 135                 140
Cys Leu Asp Val Ala Asn Gly Tyr Ser Glu His Phe Val Glu Phe Val
145                 150                 155                 160
Lys Asp Val Arg Lys Arg Phe Pro Gln His Thr Ile Met Ala Gly Asn
                165                 170                 175
Val Val Thr Gly Glu Met Val Glu Glu Leu Ile Leu Ser Gly Ala Asp
            180                 185                 190
Ile Ile Lys Val Gly Ile Gly Pro Gly Ser Val Cys Thr Thr Arg Lys
        195                 200                 205
Lys Thr Gly Val Gly Tyr Pro Gln Leu Ser Ala Val Met Glu Cys Ala
    210                 215                 220
Asp Ala Ala His Gly Leu Lys Gly His Ile Ile Ser Asp Gly Gly Cys
225                 230                 235                 240
Ser Cys Pro Gly Asp Val Ala Lys Ala Phe Gly Ala Gly Ala Asp Phe
                245                 250                 255
Val Met Leu Gly Gly Met Leu Ala Gly His Ser Glu Ser Gly Gly Glu
            260                 265                 270
Leu Ile Glu Arg Asp Gly Lys Lys Tyr Lys Leu Phe Tyr Gly Met Ser
        275                 280                 285
Ser Glu Met Ala Met Lys Lys Tyr Ala Gly Gly Val Ala Glu Tyr Arg
    290                 295                 300
Ala Ser Glu Gly Lys Thr Val Glu Val Pro Phe Lys Gly Asp Val Glu
305                 310                 315                 320
His Thr Ile Arg Asp Ile Leu Gly Gly Ile Arg Ser Thr Cys Thr Tyr
                325                 330                 335
Val Gly Ala Ala Lys Leu Lys Glu Leu Ser Arg Arg Thr Thr Phe Ile
            340                 345                 350
Arg Val Thr Gln Gln Val Asn Pro Ile Phe Ser Glu Ala Cys
        355                 360                 365
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SCHAFER, Administrative Patent Judge, concurring.

I join in the majority's opinion on priority, but write separately because I would hold, as an alternative basis for decision, that Shyamala's corresponding claims are not patentable. The utility requirement demands more than some trifling use. The use must be specific, credible, and substantial. Brenner v. Manson, 383 U.S. 519, 534 (1966). Shyamala's purported utility, tissue-typing, is not credible or substantial. Indeed, the assay in question does not even identify the tissue type. Instead, it distinguishes between muscle tissue like cardiac and striated muscle on the one hand, and other tissues, specifically brain, kidney, liver, lung, pancreas, and spleen tissue. It has long been routine to distinguish between muscle and non-muscle tissue using a microscope. Shyamala's specification offers no hint as to why one skilled in the art would go to all the trouble of probing for otherwise useless MIP mRNA when the standard microscopic method is cheaper, known to be reliable, and within the routine skill of a home hobbyist. In short, the purported utility for Shyamala's remaining claims is neither substantial nor credible. One can only wonder why Hillman did not do more to develop this issue, but Hillman's inaction does not make Shyamala's claims patentable.

Richard E. Schafer

RICHARD E. SCHAFER
Administrative Patent Judge